REMARKS

FORMAL MATTERS:

Claims 5-7, 19-22, 24-29, 31-41 are pending after entry of the amendments set forth herein.

Claim 1 is canceled without prejudice.

Claims 5, 19, 20, and 31 are amended to depend from claim 32.

Claims 22 is amended for clarity.

Claims 33-41 are added. Support for these amendments is found throughout the specification, and particularly at, for example, page 10, line 26 to page 11, line 6 and Fig. 1, as well as in claims 1, 5-7, 19-21, 24-29 and 32 as originally filed or as previously presented.

No new matter is added.

INTERVIEW SUMMARY

Applicants are grateful to Examiners Chernyshev and Ulm for the interview conducted in-person with the undersigned and Eddie Baba, as well as with Jim Diehl by telephone, on October 18, 2004. The rejections as previously applied to the pending claims were discussed, including the rejections under §101 and §112, ¶1 for written description and enablement. The Examiners requested further clarification of the data presented in the Declaration by Yasumichi Hitoshi Under 37 C.F.R. §1.132, which was filed with the response mailed February 4, 2003 (the "Hitoshi Declaration").

REJECTIONS UNDER §101 / §112, ¶1

Claims 1, 5-7, 19-22, 24-29, and 31-32 were rejected on the grounds that the claimed invention is drawn to an invention with no apparent or disclosed utility as required under §101 and further is not enabled under §112, ¶1. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

The claimed polynucleotides are useful as a probe in distinguishing breast cancer cells from normal breast cells

Applicants have presented in prior responses the reasoning and the data in support of the asserted utility of the claimed polynucleotides as probe for distinguishing a cancerous breast cell from a normal breast cell. Applicants' position is maintained, and need not be repeated here in detail.

The data in the Hitoshi Declaration was discussed during the interview with Examiners Chernyshev and Ulm. The Examiners requested that Applicants provide additional data to provide "better support" of the assertion that the claimed polynucleotides are useful as tumor markers. However, on review of the data presented, applicants respectfully submit that the data on record is sufficient to support the asserted utility.

The relevant portion of Dr. Hitoshi's declaration states:

> 13. Expression of 2.2412 was examined using a Taqman Assay. Matched tumor and normal cDNAs from lung and breast tissue were obtained from two different sources: BioChain Inc. and Clontech (clinical histories of Clontech cDNAs were not available). Location of the primers within the 2.2412 (TaHo) sequence are indicated as bolded and underlined sequences in Exhibit 2. In addition, the TaHo sequence was aligned with the Tankyrase sequence in order to demonstrate the specificity of the Taqman analysis using these primers for Tankyrase homologue. Analysis was done in triplicate and standard errors for normal and tumor tissue were determined. Expression levels in the matched samples were normalized to Ribosomal Protein S9 (S9) and the 23kD Highly Basic Protein (HBP).
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> 14. The results of these studies are shown in Exhibit 3. As shown in the graphs, 2.2412 is expressed at significantly higher levels in two types of lung cancer (bronchioalveolar carcinoma and large cell carcinoma) relative to normal lung tissue. 2.2412 is also expressed at significantly higher levels in three types of breast cancer (invasive ductal carcinoma, intraductal carcinoma and invasive lobular carcinoma) compare to normal breast tissue.

From this description it is apparent that the assays described in the Hitoshi Declaration were performed on tissues from the breast cancers listed in the graph in Exhibit 3 – invasive ductal carcinoma intraductal carcinoma, and invasive lobular carcinoma – as well as with normal breast tissue as a control. Each of these assays were performed in triplicate. In order to ensure that the differential expression observed was not due to differences in the cell types, the results were normalized to expression levels of two different "housekeeping" genes – ribosomal protein S9 (S9) and 23kD highly basic protein (HBP). In each of the three different types of breast cancer – and when normalized against two different internal controls – the data showed that 2.2412 is expressed at significantly higher levels in a breast cancer cell

than in a normal breast cell (note error bars on each column). For convenience, the data from Exhibit 3 of the Hitoshi Declaration relevant to the use of the polynucleotides in detection of breast cancer is provided in the Exhibit submitted herewith.

Applicants respectfully submit that this data is sufficient additional support for the utility asserted in the specification.

The Office Action has taken the position that, as a matter of law, the claimed invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. Thus, the Office Action concludes, "any reliance on data additionally supplied by the Declaration of Hitoshi is considered to be insufficient to overcome the instant rejection." (Office Action, page 4)

Applicants respectfully submit that, as described in detail in prior responses, the specification asserts that polynucleotides of the claimed invention are useful as probes to detect a cancerous cell, and particularly a breast cancer cell. This is not simply applicants' bare assertion – this is an assertion supported by evidence provided by the Hitoshi Declaration. Specifically, Dr. Hitoshi states in his declaration:

> **8. Given that 2.2412 specifically binds Grb14 and specifically binds Grb7, each which were known at the time the application was filed (September 23, 1997) to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed (specification page 5, lines 13-16).**
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> **9. In my opinion, the '196 application sets out a credible association of 2.2412 expression and human cancers.**

Dr. Hitoshi's conclusions above were drawn solely from the information in the specification as filed. The additional evidence provided in the Hitoshi Declaration only ***further supports the utility asserted in the specification.***

Applicants respectfully submit that the asserted utility in the use of the claimed polynucleotides as probes to distinguish cancerous breast cells from normal breast cells satisfies the requirements of §101, and meets the enablement requirements of §112, ¶1.

The claimed polynucleotides are useful for distinguishing breast cancer cells from normal breast cells since they encode a 2.2412 domain that binds to Grb7 and to Grb14, each of which are known to be differentially expressed in breast cancer cells relative to normal breast cells

Both Grb7 and Grb14 were known prior to the filing of the present invention to be differentially expressed in human breast cancer cells compared to normal breast cancer cells. The claimed polynucleotides encode polypeptides that specifically bind Grb7 and Grb14. The specification provides data in support of this assertion. Therefore, the claimed polynucleotides have a specific, substantial and credible utility in that the polynucleotides encode polypeptides that can be used to detect Grb7 and Grb14 and assess levels of these proteins in breast cells so as to distinguish normal breast cells from cancerous breast cells.

Specifically, at page 10, line 26 to page 11, line 6, the specification describes a study conducted to determine the region of the 2.2412 polypeptide that binds to Grb7 and to Grb14. cDNAs encoding the "full-length", N- or C-terminal regions of the polypeptide of the "original" 2.2412 clone were used in GST-fusion protein constructs. This "original" 2.2412 clone encoded only a portion of SEQ ID NO:2 (from nucleotides 694-2664 of SEQ ID NO:1, which encode amino acids 232-888 SEQ ID NO:2). The N-terminal portion of this clone corresponded to nucleotides 694-1614 of SEQ ID NO:1, which encode amino acid residues 232-538 of SEQ ID NO:2. The C-terminal portion corresponded to nucleotides 1615-2664 of SEQ ID NO;1, which encode amino acid residues 539-888.

The fusion proteins were then incubated with detectably labeled Grb14 or human breast cancer cells expressing high levels of Grb7. Both Grb14 and Grb7 were known to be differentially expressed in breast cancer as noted in the specification (see page 2, lines 25-30), and further as disclosed in the art prior to the filing date of the invention.[1]

As discussed in the specification at page 11, lines 3-6, the data showed that the fragment of the 2.2412 encoded by the "original" clone (amino acids 232-888 of SEQ ID NO:2) specifically bound Grb7 and specifically bound Grb14. The N-terminal portion (amino acids 232-538) bound to Grb7 and Grb14 more strongly than the C-terminal portion, indicating that the N-terminus contains a domain that mediates Grb7/Grb14 binding by the 2.2412 fragment encoded by the "original" clone.

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[1] See, e.g., Daly et al. 1996 J. Biol. Chem. 271:12502-10; Stein et al. 1994 EMBO J 13:1331-40 (copies previously submitted) with response filed February 4, 20023).

Applicants respectfully submit that the asserted utility of 2.2412 polypeptides and Grb7/Grb14-binding fragments in distinguishing cancerous breast cells from normal breast cells is a utility that satisfies the requirements of §101, and is fully enabled within the requirements of §112, ¶1. It then follows that polynucleotides encoding such polypeptides also satisfy the requirements of these statutes.

In view of the above, withdrawal of the rejections under §101 and §112, ¶1 are respectfully requested.

REJECTIONS UNDER §112, ¶1 – WRITTEN DESCRIPTION

Claims 1, 5-7, 20, 22, 24-26, and 28 were rejected on the grounds that these claims contain subject matter not adequately described in the specification so as to satisfy the written description requirement of §112, ¶1. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

Applicants note that none of claims 19, 21, 27, 29, 31 and 32 has not been rejected as not being supported by an adequate written description. Applicants thus presume that the Office has determined that these claims satisfy the written description requirement of §112, ¶1. Since claims 5-7 and 20 are amended to depend from claim 32, these claims likewise meet the written description requirement and for at least this reason the rejection as applied to claims 5-7 and 20 should be withdrawn.

As to the remaining claims, applicants respectfully disagree with the Office's position. The Office has responded to applicants' prior response by stating that "there appears to be no clear correlation between structure of the repeats and the ability to bind Grb7 and to function as a tumor marker." (Office Action page 5) However, the specification does provide such guidance.

The specification provides a correlation between structure of the 2.2412 polypeptide and its function in binding Grb7 and Grb14

The specification provides guidance as to the correlation between 2.2412 structure and Grb7/Grb14 binding. At page 10, line 26 to page 11, line 6, the specification describes a study conducted to determine the region of the 2.2412 polypeptide that binds to Grb7 and to Grb14. cDNAs encoding the "full-length", N- or C-terminal regions of the polypeptide of the "original" 2.2412 clone were used in GST-fusion protein constructs. This "original" 2.2412 clone in fact only encoded a portion

of SEQ ID NO:1 (from nucleotides 694-2664, which encodes amino acids 232-888). The N-terminal portion of this clone corresponded to nucleotides 694-1614 of SEQ ID NO:1, which in turn encodes amino acid residues 232-538 of SEQ ID NO:2. The C-terminal portion corresponded to nucleotides 1615-2664 of SEQ ID NO;1, which in turn encodes amino acid residues 539-888.

The fusion proteins were then incubated with detectably labeled Grb14 or human breast cancer cells expressing high levels of Grb7. The data showed that the fragment of the 2.2412 encoded by the "original" clone (amino acids 232-888 of SEQ ID NO:2) specifically bound Grb7 and specifically bound Grb14 (specification page 11, lines 3-6). Furthermore, the N-terminal portion (amino acids 232-538) bound to Grb7 and Grb14 more strongly than the C-terminal portion, thus showing that the N-terminus contains the binding domain of the 2.2412 fragment encoded by the "original" clone. This structure of the 2.2412 polypeptide corresponds to the function of the 2.2412 polypeptide in Grb7/Grb14 binding.

Given this description in the specification, there is more than adequate information provided as to a correlation between structure and function for 2.2412 in binding Grb7 and Grb14.

The specification provides adequate description of sequences that can function as probes within the scope of the claims

The specification discloses both a nucleotide sequence (SEQ ID NO:1) and the amino acid sequence it encodes (SEQ ID NO:2). The specification discloses that sequences having at least 95% sequence identity are within the scope of the invention (see, e.g., specification page 3, lines 8-10). The specification also discloses that the invention contemplates probes that selectively hybridize to 2.2412-encoding polynucleotides under high stringency conditions (see, e.g., specification page 4, lines 19-25).

The correlation between structure of a given sequence and its function as a probe for detection of a polynucleotide is well known. Further, here the claims encompass not just any polynucleotide with any level of sequence identity, but instead encompass those polynucleotides that have *at least 95% sequence identity to a recited nucleotide sequence*. The ordinarily skilled artisan would recognize given the disclosure above that polynucleotides having at least 95% sequence identity to a recited nucleotide sequence, and further where the open reading from of that sequence is provided, are described in the instant specification.

In other words, disclosure of SEQ ID NO:1 and its encoded amino acid sequence SEQ ID NO:2, identification of domains of the encoded amino acid sequence, **and** identification of an amino acid sequence region that mediates Grb7?Grb14 binding provide sufficient disclosure to the ordinarily skilled

artisan as to the polynucleotides that are useful as probes for detection of a 2.2412-encoding polynucleotide and have at least 95% sequence identity to the sequence recited in the claims. For example, even simply changing the nucleotide sequence to take into account the degeneracy of the genetic code based on the disclosure of the encoded amino acid sequence in Fig. 1 (SEQ ID NO:2) provides ample disclosure to the ordinarily skilled artisan of sequences having at least 95% sequence identity to the sequences recited in the claims. .

In view of the above, withdrawal of rejection under §112, ¶1 (written description) is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-012.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Jan 26, 2005

By: _____
Carol L. Francis
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Enclosure: Exhibit

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